Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Review

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Product Name(s):	Singulair (montelukast)
Subject:	Neuropsychiatric events and Churg-Strauss Syndrome
Application Type/Number:	NDA 204804 NDA 021409 NDA 020830 NDA 020829
Submission Number:	Original Submission
Applicant/Sponsor:	Merck Consumer Care, Inc. Merck & Co, Inc.
OSE RCM #:	2013-2360

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates the FDA Adverse Event Reporting System (FAERS) database and published literature for serious events reported with montelukast including death, neuropsychiatric events, and Churg-Strauss Syndrome (CSS). Safety concerns have been raised and addressed by the FDA in the past regarding the increased risk of neuropsychiatric adverse events, including suicide and suicide attempts, and CSS associated with the use of montelukast. The Division of Nonprescription Clinical Evaluation (DNCE) requested this review to update the previous Division of Pharmacovigilance (DPV) reviews of these events and inform a New Drug Application (NDA) submitted by Merck Consumer Care, Inc. (Merck), which requests a partial switch of montelukast to nonprescription status for the temporary relief of allergy symptoms in adults 18 years and older.

The FDA (the Division of Pulmonary, Allergy, and Rheumatology Products and Office of Surveillance and Epidemiology) previously conducted several scientific reviews for all ages using data from the pre-market clinical trials and data from FAERS and literature to assess the association of neuropsychiatric events and CSS with montelukast use. These FDA reviews concluded that the clinical details of some post-marketing reports involving montelukast appeared consistent with a drug-induced effect. Labeling for both neuropsychiatric events (including suicide) and CSS appear in the Warnings and Precautions section of the current montelukast prescribing information.

To update previous reviews, a search of the entire FAERS database identified a total of 11,649 reports with montelukast from approval (1998) to October 31, 2013. Seventy-six percent of all reports indicated a serious outcome, and death was reported as an outcome in approximately 5% of the total FAERS reports for montelukast. Completed suicide was reported in 1.6% of the total montelukast FAERS reports. Asthma was the most frequently reported indication, followed by allergy-related indications. Additionally, the most frequently reported preferred terms (PTs) included depression, suicidal ideation, allergic granulomatous angiitis, and abnormal behaviour. The median age was 31 years for the total FAERS report series. The median age was 45 years old for the completed suicide report series; however, in the neuropsychiatric reports (excluding completed suicide), it was 11 years old. In patients less than 18 years of age, death was reported as an outcome in 19% of the report series, and CSS was reported with montelukast in 5% of the report series. These ages are consistent with previous FDA reviews of neuropsychiatric events with montelukast use.

Both age and indication were consistent with recent drug utilization data for montelukast. Based on the drug utilization data, adults accounted for the majority (58%) of montelukast patients, followed by pediatric patients aged 0-17 years old at approximately 43% of total patients. Moreover, from year 2002 to 2012, asthma was the top diagnosis associated with the use of montelukast among all patient age groups, followed by allergic rhinitis.[1]

The FAERS reports of neuropsychiatric events were mostly from the US. The most frequently reported neuropsychiatric PT when montelukast was used for allergy-related indication was abnormal behaviour and for asthma-related indication was suicidal ideation. Most of the neuropsychiatric PTs reported are labeled events with the exception of crying. However, crying may be a manifestation of reported PT terms Irritability and Mood swings. Although a

mechanism of action for montelukast causing these neuropsychiatric events is unknown at the present time, patients and healthcare providers are advised to monitor for symptoms and to consider discontinuation of the drug in the event of these symptoms occurring.

The neuropsychiatric events identified in this review are labeled in the prescribing information and the proposed over-the-counter (OTC) Drug Facts label with similar terms to those preferred terms reported in this review.

In addition to FAERS, we reviewed the literature and dataming results. The majority of potential signals through data mining for montelukast were related to either CSS or neuropsychiatric events, which have all been labeled with no additional or new safety signals. A literature search was conducted from January 1, 2012, until December 18, 2013, to update previous literature reviews. This literature review did not reveal any new evidence regarding serious events or safety concerns associated with the use of montelukast. However, a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level was noted. This runs parallel to the joint statement made by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI), and previous conclusions from prior Office of Surveillance and Epidemiology reviews.

Of note, the numbers in this review represent crude counts and were not further evaluated for an association with montelukast since the association of these events with montelukast use is well-documented. In addition, this review does not indicate any increased trend in severity or frequency of reporting of neuropsychiatric events or CSS since previous reviews. However, a spike in reports was noted in 2008, which may have been a result of stimulated reporting after the release by the FDA of an Early Drug Safety Communication notifying the public of the potential association of neuropsychiatric events with montelukast use.

Reports of CSS with montelukast continue to be submitted to FAERS with a total of 884 reports since approval. A majority of the reports were in adults and indicated for asthma, which is consistent with CSS etiology. These reports were not further evaluated for an association with montelukast since the potential association of CSS with montelukast is well-documented even though a mechanism of action for this association has not been identified.

The current montelukast prescribing information adequately informs healthcare professionals of the potential association with CSS. The montelukast patient information sheet provided with the prescription also adequately informs patients, in consumer-friendly language, of CSS. In contrast, the proposed OTC Drug Facts label for montelukast does not offer any information for consumers about the potential association with CSS, symptoms of CSS, or what to do if symptoms develop. Although the majority of FAERS reports of CSS with montelukast use reported asthma as the indication for montelukast and the proposed indication for OTC montelukast is relief of allergy symptoms, the potential exists that patients with asthma may use OTC montelukast. CSS is a life-threatening condition. In general, early diagnosis of CSS improves survival, which increases the importance of including labeling for CSS.

In summary, a review of post-marketing data for montelukast did not identify any new safety issues that have not been previously recognized and reviewed by the FDA. The crude count analyses of up-to-date FAERS data on CSS and neuropsychiatric events are consistent with the current labeling.

Although approvability of an OTC montelukast product is beyond the scope of this review, DPV agrees with the proposed labeling for neuropsychiatric events on the OTC montelukast Drug Facts label submitted with NDA 204804, but the Drug Facts label lacks information about CSS. DPV recommends the following for consideration:

- If approved, add a statement to the OTC montelukast Drug Facts label Warnings Section for Churg-Strauss Syndrome using language that is similar to language found in the prescription montelukast Patient Information.

1 INTRODUCTION

This review evaluates the FDA Adverse Event Reporting System (FAERS) database and published literature for serious events reported with montelukast including death, neuropsychiatric events, and Churg-Strauss Syndrome. The Division of Nonprescription Clinical Evaluation (DNCE) requested this review to inform a New Drug Application (NDA) submitted by Merck Consumer Care, Inc. (Merck), which requests a partial switch of montelukast to nonprescription status for the for the temporary relief of allergy symptoms in adults 18 years and older.

1.1 BACKGROUND

On September 6, 2013, Merck submitted an NDA requesting a partial switch of montelukast 10 mg tablets (proposed tradename Singulair Allergy) from prescription to over-the-counter (OTC). The proposed OTC indication is for the temporary relief of allergy symptoms (sneezing, runny nose, itchy nose, watery eyes, itchy eyes, and nasal congestion) related to hay fever or other upper respiratory allergies in adults 18 years of age and older. This is not a full nonprescription switch since the prescription montelukast is also indicated for: the prophylaxis and chronic treatment of asthma in patients ≥ 12 months of age; acute prevention of exercise-induced bronchoconstriction in patients ≥ 6 years of age; and relief of symptoms of allergic rhinitis (seasonal in patients ≥ 2 years of age and perennial in patients ≥ 6 months of age).

DNCE requested this review of post-marketing montelukast safety data to aid in the decision to approve the switch to nonprescription status. Montelukast is a leukotriene receptor antagonist which has been associated with neuropsychiatric adverse events in all age groups. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) and the Office of Surveillance and Epidemiology (OSE) have reviewed this association previously (tracked safety issue number 415) after supplements were submitted by Merck in 2007 to add several different neuropsychiatric events to the post-marketing adverse event section of the montelukast prescribing information. (OSE's reviews are summarized below in section 1.2) Additionally, on October 22, 2007, correspondence was received by the FDA from New York State Senator Elizabeth Little, which requested the FDA review the safety of montelukast after a 15 year old living in her district committed suicide 17 days after starting montelukast. The OSE and DPARP reviews resulted in the addition of neuropsychiatric events to the Precautions section (currently Warnings and Precautions section, see section 1.4 of this review) of the montelukast prescribing information and patient information sheet. Several Drug Safety Communications were also posted on the FDA internet to inform healthcare professionals and patients of the new safety information.[2,3]

The safety of montelukast was further reviewed after a Citizen Petition was submitted by the Parents United for Pharmaceutical Safety and Accountability on September 28, 2008 (FDA-2009-P-0039). The Petition requested the FDA remove the indication for montelukast use in children and requested labeling changes for the following adverse events: seizures, neurological damage, neuropsychiatric events, and Churg-Strauss Syndrome (CSS). DPARP and OSE opened a track safety issue for the Petition (number 837), and reviewed these safety issues (the OSE

review is summarized below in section 1.2). The reviewers concluded the montelukast labeling to be adequate for the concerns raised by the Petition.[4] FDA denied the Petition's request to remove the indication for use in children, but added Henoch-Schönlein purpura, a form of systemic vasculitis, to the Adverse Reactions, Post-marketing Experience section of the label.

1.2 PREVIOUS POSTMARKETING REVIEWS

Previous reviews by OSE:

- 12/22/05 OSE Postmarketing Safety Review Congenital Anomaly-limb Reduction Defect[5] Epidemiological analyses did not support an association between montelukast and limb reduction defects.
- 12/19/08 (RCM # 2008-474) OSE AERS Postmarketing Safety Review: Mood, Cognitive, Perception, Sleep and Movement Adverse Events[6] Mood (including suicide and suicidal ideation), cognitive, perception, and sleep adverse events were reviewed for an association with montelukast use. This review was initiated by an inquiry to FDA from New York State Senator Little on behalf of a constituent. The 15-year-old son of this constituent committed suicide, in August 2007, while taking montelukast to treat allergic rhinitis. The Recommendation listed: Neuropsychiatric events should be added to the Precautions section (currently Warnings and Precautions section) of the label.
- 06/30/10 (RCM# 2010-1209) Labeling Submission for 'disorientation' OSE[7] Disorientation reviewed for an association with montelukast use. Recommended disorientation be labeled based on Changes Being Effected (CBE).
- 11/17/10 (RCM# 2010-680) OSE Review of fatal anaphylaxis, serious skin reactions, immune thrombocytopenia[8] These events were reviewed and it was recommended to label thrombocytopenia only.
- 05/14/11 (RCM #2009-1006) Citizens Petition OSE[9] Consult received from the Office of Regulatory Policy. The Petitioner requested: remove the montelukast indication for use in children, changes to the product labeling, implement requirements that adverse events are reported by physicians, and that all labeling changes are communicated to consumers. This OSE review evaluated neuropsychiatric events (vocal and motor tics, seizures and brain damage, status epilepticus, death) and vasculitis (vasculitides, deaths, Churg-Strauss syndrome) with montelukast use. The reviewer recommended no labeling changes to the product labeling were necessary at that time.
- 05/12/12 (RCM# 2012-512) OSE Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) (TSI 1310)[10] Review was based upon the Japanese Pharmaceuticals and Medical Devices Agency update of the montelukast label to include TEN and SJS. The reviewer recommended adding SJS/TEN to the montelukast label.
- 02/27/13 (RCM# 2012-1478) OSE Association between leukotriene-modifying agents (LTMA) and suicide[11] This review evaluated a newly published nested case-control study. The reviewer concluded that well-designed epidemiologic studies are lacking to quantify the suicide risk related to use of LTMAs. No need for further regulatory action by FDA.

1.3 REGULATORY HISTORY

The FDA first approved montelukast on February 20, 1998, for the prophylaxis and chronic treatment of asthma in patients 15 years and older (10 mg tablets/NDA 020829) and ages 6 to 14 years (4 and 5 mg chewable tablets/NDA 20830). Subsequent indications include: prophylaxis

of asthma in 2 to 5 years of age (3/3/2000), treatment of asthma in 12 months and older (7/26/2002), relief of symptoms of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older (12/31/2002), relief of symptoms of perennial allergic rhinitis (PAR) in adults and pediatric patients 6 month of age and older (7/27/2005), prevention of exercise-induced bronchoconstriction in patients 15 years of age and older (4/13/2007), and prevention of exercise-induced bronchoconstriction in patients 6 to 14 years of age (3/26/2012). Montelukast is available as 5-mg and 10-mg film-coated tablets, 4-mg and 5-mg chewable tablets, and 4-mg oral granules.

1.4 PRODUCT LABELING

The *Prescribing Information*[12] for montelukast contains the following information regarding neuropsychiatric events and Churg-Strauss in the Warnings and Precautions, Adverse Reactions, and Patient Counseling Information sections of the label:

> ***Neuropsychiatric Events***
> Neuropsychiatric events have been reported in adult, adolescent, and pediatric patients taking montelukast sodium. Post-marketing reports with montelukast sodium use include agitation, aggressive behavior or hostility, anxiousness, depression, disorientation, disturbance in attention, dream abnormalities, hallucinations, insomnia, irritability, memory impairment, restlessness, somnambulism, suicidal thinking and behavior (including suicide), and tremor. The clinical details of some post-marketing reports involving montelukast sodium appear consistent with a drug-induced effect.
>
> Patients and prescribers should be alert for neuropsychiatric events. Patients should be instructed to notify their prescriber if these changes occur. Prescribers should carefully evaluate the risks and benefits of continuing treatment with montelukast sodium if such events occur,
>
> Patients should be instructed to notify their physician if neuropsychiatric events occur while using montelukast sodium.
>
> ***Eosinophilic Conditions***
> Patients with asthma on therapy with montelukast sodium may present with systemic eosinophilia, sometimes presenting with clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition which is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction of oral corticosteroid therapy. Physicians should be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal association between montelukast sodium and these underlying conditions has not been established.

These events are also described in the FDA approved Patient Information sheet for Singulair below.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:

• agitation including aggressive behavior or hostility • attention problems • bad or vivid dreams • depression • disorientation (confusion) • feeling anxious • hallucinations (seeing or hearing things that are not really there)	• irritability • memory problems • restlessness • sleep walking • suicidal thoughts and actions (including suicide) • tremor • trouble sleeping

- **Increase in certain white blood cells (eosinophils) and possible inflamed blood vessels throughout the body (systemic vasculitis).** Rarely, this can happen in people with asthma who take SINGULAIR. This sometimes happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.
  Tell your healthcare provider right away if you get one or more of these symptoms:
  - a feeling of pins and needles or numbness of arms or legs
  - a flu-like illness
  - rash
  - severe inflammation (pain and swelling) of the sinuses (sinusitis)

Selected sections of the Patient Information sheet are included in Appendix B.

The proposed OTC Drug Facts label submitted September 6, 2013, as part of the NDA for Singulair Allergy includes:

Uses: temporarily relieves these symptoms due to hay fever or other upper respiratory allergies: nasal congestion; runny nose; itchy, watery eyes; sneezing; itching of the nose

Warnings: Do not use to treat asthma. Asthma can be a life-threatening condition, and you should follow your doctor's directions.

Do not use:

- With any other drug containing montelukast sodium. If you are not sure whether a drug contains montelukast sodium, ask a doctor or pharmacist.
- if you are allergic to montelukast sodium or any of the interactive ingredients of this product

When using this product

- if you have asthma and allergies, you can use this product for your allergies if you are not taking another drug containing montelukast sodium
- if you are currently taking asthma medicines, do not stop taking them

Stop use and ask a doctor if

- you experience unexpected changes in thoughts, behaviors and moods
- you experience unexpected changes or problems when you sleep
- an allergic reaction to this product occurs. Seek medical help right away.

If pregnant or breastfeeding, ask a health professional before use.

Directions:

- use every day, only during the time you are suffering from allergies, for best results
- adults 18 years of age and older: take 1 tablet daily; not more than 1 tablet in 24 hours
- children under 18 years of age: do not use

In addition, Merck has proposed to include a Consumer Information Leaflet with OTC Singulair Allergy, which Merck submitted on October 29, 2013, as part of the NDA. This Consumer Information Leaflet further addresses the neuropsychiatric events that are found in the prescription montelukast prescribing information and instructs consumers to stop use and talk to their doctor if they experience any of these events. The Consumer Information Leaflet submission lists the neuropsychiatric events identified in the prescription Singulair Patient Information Sheet; however, Merck states they would like to further discuss with DNCE what would be the most appropriate events for the OTC Consumer Information Leaflet.

2 OVERVIEW OF POST-MARKETING DATA WITH MONTELUKAST

2.1 METHODS AND MATERIALS

2.1.1 FAERS Search Strategy

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.

Table 1. FAERS Search Strategy*	
Date of search	December 12, 2013
Time period of search	February 20, 1998^ - October 31, 2013
Product Terms	Active ingredient: Montelukast, Montelukast sodium

* See Appendix A for description of the FAERS database.
^ FAERS searched from US Approval to data lock date for this review

2.1.2 Data Mining Search Strategy

The Empirica Signal database was searched with the strategy described in Table 2.

Table 2. Data Mining Search Strategy*	
Data Refresh Date	December 5, 2013
Product Terms	Montelukast
Empirica Signal Run Name	Generic By Suspect Drugs only
MedDRA Search Strategy	PT terms

* See Appendix A and C for description of Data Mining of FAERS using Empirica Signal.

2.1.3 Literature Search

The medical literature was searched with the strategy described in Table 3.

Table 3. Literature Search Strategy	
Date of search	December 18, 2013
Database	PubMed@FDA, Google, Google Scholar
Search Terms	Singulair, Montelukast, Leukotriene-Modifying Agents, Neuropsychiatric Events, Suicide, Suicidal Ideation, Depression, Agitation, Anxiety, Aggressive Behavior, Hallucinations, Disorientation, and Churg-Strauss Syndrome
Years included in search	January 1, 2012-December 18, 2013
Languages	English, French

2.2 RESULTS

2.2.1 Overview of FAERS Montelukast Reports

The search identified 11,649 postmarketing reports associated with montelukast in the FAERS database (crude counts). Table 4 summarizes the crude counts of all FAERS reports with montelukast from approval, February 20, 1998, to October 31, 2013. This table uses a crude count of reports. These reports have not been assessed for an association with montelukast and may contain duplicate reports.

Table 4. Crude Counts* of FAERS Reports with Montelukast use, received by FDA from Approval to October 31, 2013 (N=11649)		
Age (N=9146)	Mean	33 years
	Median	31 years
	Range	2 days-102 years
	<18 years	3892 (43%)
Sex (N=10846)	Male	4640
	Female	6206
Initial FDA Received Date	1998	218
	1999	874
	2000	814
	2001	557
	2002	318
	2003	373
	2004	409
	2005	428
	2006	478
	2007	394
	2008	1796
	2009	949
	2010	686
	2011	554
	2012	917
	2013	1883
Event Date (N=7811)	1989	2
	1990	1
	1992	3
	1996	3
	1997	11
	1998	513
	1999	528
	2000	548
	2001	368
	2002	292
	2003	365
	2004	352
	2005	424

	2006	456
	2007	595
	2008	1049
	2009	635
	2010	431
	2011	418
	2012	523
	2013	294
Country of reporter	United States	8355
	Foreign	3294
Report type (N=11648)	Expedited	6894
	Direct	2401
	Periodic	2353
Serious Outcomes[†] (N=8846)	Death	567
	Life-threatening	982
	Hospitalized	3127
	Disability	856
	Congenital anomaly	105
	Other serious	5128
Frequently reported PTs[‡,§]	Depression (1054), suicidal ideation (981), allergic granulomatous angiitis (884), abnormal behaviour (821), aggression (811), anxiety (751), asthma (715), headache (584), insomnia (647), dyspnoea (503), fatigue (439), anger (421), crying (421), nightmare (410)	
Most frequently reported PTs in reports with serious outcomes[‡.§] (N=8846)	Suicidal ideation (893), allergic granulomatous angiitis (875), depression (862), aggression (659), abnormal behaviour (625), anxiety (592), asthma (588), insomnia (417)	
Primary suspect medication	Montelukast (10538), other medications (1111)	
Most frequent indication for montelukast use[‖] (N=8209)	Asthma (6186), hypersensitivity (779), multiple allergies (629), rhinitis allergic (387), seasonal allergy (228)	

[*] May include duplicates

[†] Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events. Reports may include multiple outcomes.

[‡] Each report may have multiple PTs

[§] PTs with ≥ 400 occurrences

[‖] Indications with ≥ 200 occurrences

The FAERS search identified 11,649 reports with montelukast from approval to October 31, 2013. Seventy-six percent (8846/11649) of all reports indicated a serious outcome. Spikes in reporting were noted in the years 2008 and 2013; however, review of event dates associated

with these reports show a spike in 1998 (year of approval) and 2008. The 2008 spike could be due to stimulated reporting as a result of the Early Communication released by the FDA that discusses the neuropsychiatric events with montelukast. A review of event dates does not reveal a spike of events in 2013. The majority of reports submitted in 2013 reported events prior to 2013.

Preferred Terms related to neuropsychiatric events were most frequently reported, with depression and suicidal ideation topping the list. The preferred term allergic granulomatous angiitis (also known as Churg-Strauss Syndrome) was also frequently reported. Seventy-five percent (6186/8209) of the reports that provided information on indication for montelukast documented asthma.

2.2.2 Deaths

Table 5 summarizes the 567 FAERS reports which reported death as an outcome. This table uses a crude count of reports. These reports have not been assessed for an association with montelukast and may contain duplicate reports.

Table 5. Crude Counts* of FAERS Reports with Montelukast use and reporting an outcome of Death, received by FDA from February 20, 1998 to October 31, 2013* **(N=567)**		
Age (N=470)	Mean	47 years
	Median	53 years
	Range	0 – 94 years
	<18 years	90 (19%)
Sex	Male	214
	Female	294
	Unknown	59
Initial FDA received date	1998	24
	1999	22
	2000	25
	2001	29
	2002	23
	2003	25
	2004	21
	2005	32
	2006	10
	2007	11
	2008	84
	2009	45
	2010	22
	2011	34
	2012	53
	2013	107
Event date (n=315)	1998	28

	1999	18	
	2000	20	
	2001	20	
	2002	21	
	2003	18	
	2004	14	
	2005	23	
	2006	27	
	2007	30	
	2008	25	
	2009	17	
	2010	24	
	2011	12	
	2012	12	
	2013	6	
Country of reporter	United States	387	
	Foreign	180	
Report type	Expedited	514	
	Direct	49	
	Periodic	4	
Frequently reported PTs[^†] (N=381)	Completed Suicide		196
	Death		62
	Asthma		49
	Toxicity to various agents		45
	Abortion Spontaneous		37
	Pregnancy		28
	Maternal drug affecting foetus		26
	Cardio-respiratory arrest		24
	Depression		22
	Cardiac arrest		21
Primary suspect medication	Montelukast	428	
	Other medications	139	
Most frequent indication for montelukast use[††] (N=547)	Unknown	260	
	Asthma	226	
	Abuse	26	
	COPD[‡]	20	
	Allergy	15	

* These reports have not been assessed for an association with montelukast and may contain duplicates.
^ Each report may have multiple PTs
† PTs with ≥ 20 occurrences
†† Indication with ≥ 15 occurrences
‡ COPD = Chronic obstructive pulmonary disease

Death was reported as an outcome in 567 FAERS reports, which is approximately 5% of the total FAERS reports for montelukast. Reports were submitted to FDA consistently since approval in 1998; however, an increase in reports was noted in 2008 and 2013. This increase in reporting

was not consistent with the event dates reported. There was no increase in event dates noted in either 2008 or 2013. The most frequently reported preferred terms for reports with death as an outcome were related to suicide or pregnancy.

Two of the frequently reported preferred terms were related to pregnancy and miscarriage (i.e., abortion spontaneous and maternal drug affecting foetus). Montelukast is currently labeled as Pregnancy Category B based on negative animal studies and no adequate, well-controlled studies in pregnant women. After approval, Merck established an informal pregnancy registry for montelukast by including an 800 number in the montelukast prescribing information to report prenatal exposure. Many of the reports reporting adverse events related to pregnancy and miscarriage in the death report series were from the Merck pregnancy registry. Of note, in 2006, Merck, DPARP, OSE, the Maternal Health Team, the Office of Pharmaceutical Science, and independent teratologist reviewed possible teratogenic risks associated with the use of montelukast due to 6 reports of congenital limb defects in infants born to mothers prescribed montelukast during their pregnancy. A causal relationship between the teratogenic events and montelukast could not be established.[13]

Completed suicide was reported as a preferred term in 35% (196/567)[a] of the reports that reported death as outcome, and 1.6% (196/11649) of the total montelukast FAERS reports. Of the reports containing the preferred term Completed suicide and also reporting an age (n=170)[b], the median age for completed suicides was 45 years, with a range of 7 years to 79 years.

Eighty-nine of the 196 completed suicide reports were published in the Annual Report of American Association of Poison Control Centers National Poison Data System (AAPCC-NPDS). Frequently reported preferred terms for these reports included: toxicity to various agents (n=22); overdose (n=9); and cardio-respiratory arrest (n=7). These reports involved multi-drug overdoses and provided few details about the patients or their medication histories.

Since the previous OSE review of neuropsychiatric events and completed suicides with montelukast use was completed in 2008, 43 unique reports which contain the PT Completed suicide have been submitted to FAERS (excluding reports that were published in the AAPCC-NPDS annual report). Thirty-one of these reports submitted an age which ranged from 7 to 77 years. Twelve of the thirty-one reports were submitted for children (≤ 17 years).[c] Half of the reports (22/43) were submitted between June 13, 2008 (from previous OSE review) to January 1, 2010, which may be a result of stimulated reporting of the FDA communications regarding neuropsychiatric events released in 2008 and 2009.[2,3] Appendix C contains a line listing with narrative for these 43 reports.

2.2.2 Overview of Data Mining

[a]The 196 cases of completed suicide include reports previously described in the 2008 DPV review of montelukast and suicide.

[b] This number represents a crude count of reports that have not been assessed for an association with montelukast and may contain duplicate reports.

[c] Three of the twelve pediatric reports (FAERS case # 6669700; 6717135; and 7015118) appeared in the 2009 DPV review of pediatric events with Singulair for the Citizen Petition.[9]

The datamining results for montelukast are in Appendix E. The EB05 score for the top 8 PT terms (Allergic granulomatous angiitis, Mononeuritis, Pancoast's syndrome, Hypereosinophilic syndrome, Allergic respiratory disease, Eosinophilic myocarditis, Eosinophilic pneumonia, and Eosinophil count increased) are terms related to eosinophilic conditions, which are a labeled events in the Warnings and Precautions section of the montelukast label. Other PT terms with high EB05 scores include neuropsychiatric events (e.g., Sleep terror, Self-esteem decreased, Nightmare, Morbid thoughts, Suicidal ideation, and Mood altered), which are adequately described in the label.

2.2.3 Overview of Literature

Safety concerns have been raised and addressed by the FDA in the past regarding the increased risk of neuropsychiatric adverse events associated with the use of leukotriene-modifying agents, specifically, suicide and suicide attempts among patients with asthma. The FDA (Office of New Drugs and Office of Surveillance and Epidemiology) conducted several scientific reviews using data from the pre-marketing clinical trials and data from FDA's Adverse Event Reporting System (FAERS), and concluded that the clinical details of some post-marketing reports involving montelukast appeared consistent with a drug-induced effect. A labeling change to all the leukotriene-modifying agents was made in 2009 to include a precaution in the drug-prescribing information.

In February of 2013, the Division of Epidemiology (DEPI) re-evaluated the possible association between leukotriene-modifying agents and suicide by evaluating recent publications and case control studies in order to quantify the suicide/risk attempt from leukotriene-modifying agents. The review noted that published clinical trials did not identify risk of suicide from leukotriene-modifying agents, a result likely due to the small sample size and low suicide rate. The review concluded that well-designed epidemiologic studies were lacking and that none of the literature identified at the time indicated the need for further regulatory action by the FDA.[14]

For this review, an updated literature search was conducted from January 1, 2012 through December 18, 2013. A list of terms used in the search (please refer to Table 3, section 2.1.3) has not revealed any new evidence regarding serious events or safety concerns associated with the use of montelukast. The literature identified at this time does not indicate a need for further regulatory action by the FDA. Well-designed epidemiologic studies are currently lacking to quantify the level of risk of suicide/suicide attempt among asthma patients, including pediatric asthma patients, and therefore, continued monitoring of the literature is recommended.

2.3 DISCUSSION OF OVERVIEW OF POST-MARKETING DATA WITH MONTELUKAST

A review of post-marketing data for montelukast did not identify any new safety issues that have not previously been reviewed by the FDA. The most often reported safety issues are related to neuropsychiatric events and Churg-Strauss Syndrome associated with montelukast use. These events are further reviewed and discussed in sections 3 and 4 of this review.

The FAERS search identified 11,649 reports with montelukast from approval to October 31, 2013. Seventy-six percent of all reports indicated a serious outcome while 40% of all reports resulted in death, hospitalization, or were life-threatening. Death was reported as an outcome in approximately 5% (567/11649) of the total FAERS reports for montelukast. The most frequently

reported PTs included those for neuropsychiatric events: depression (n=1054), suicidal ideation (n=981), and abnormal behaviour (n=821). Completed suicide is reported in 1.6% (196/11649) of the total montelukast FAERS reports. These events are labeled in the prescribing information and the proposed OTC Drug Facts label with similar neuropsychiatric terms found in this review of FAERS. Of note, the term crying (n=421) is an unlabeled event, but could be a result of related PT terms associated with mood disturbances.

The majority of fatal reports were in adults. The median age for the death report series was 53 years and 45 years in those reporting a completed suicide.

The most frequent indication for montelukast use in the FAERS report series was asthma (53%). Allergy indications (PT: Multiple allergies, Rhinitis allergic, and Seasonal allergy) represented 10% (1244/11649) of FAERS reports.

Since the review by DEPI in 2013, there has been no new literature published regarding serious events or safety concerns with regards to suicide/suicide attempts associated with montelukast use. However, there is a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among asthma patients, including, pediatric asthma patients. This runs parallel to the joint statement made by the American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI) that "there are no data from well-designed studies to indicate a link between Singulair and suicide [and] it is unknown whether there is an increased incidence of suicide in patients receiving Singulair."[15] At this time, there is no published article that indicates a need for further regulatory action by the FDA, however, continued monitoring of the literature is recommended.

3 NEUROPSYCHIATRIC EVENTS

3.1 METHODS AND MATERIALS

To capture all the reports of neuropsychiatric events, we searched FAERS on December 12, 2013, using the FAERS search strategy in Table 1. To further characterize the reports, Empirica was used as a data managing tool. Audit trails for asthma and allergy indication PTs are in Appendix D.

1) We ran a 'Generic by Year 3D- DEI (Drug, Event, Indication) without litigation & foreign regulatory agencies removed' (ID 11247) to identify 3D combinations that cannot be explained by any of the corresponding pair-wise associations.
2) We stratified the 680 PTs coded under the Psychiatric disorders SOC by indication (allergy-related or asthma-related). Reports with a D-E-I Interaction Signal Score > 1 were selected.
3) We then removed reports with an outcome of death or PT Completed suicide.
4) The time period of search was from March 27, 2008 (Date of previous review[6] of neuropsychiatric events) to October 31, 2013.

3.2 RESULTS

Table 6 summarizes the FAERS reports of neuropsychiatric events with montelukast based on allergic and asthma-related PTs. This table uses a crude count of reports. For this review, the reports have not been assessed for an association with montelukast and may contain duplicate reports.

Table 6 . Crude Counts of FAERS Reports of Neuropsychiatric Events with Montelukast based on *allergic and asthma related* PT indications (excluding death outcome and completed suicide PT), received by FDA from March 27, 2008 to October 31, 2013.

	Indication: Allergic related PT (n=551)	**Indication: Asthma related PT (n=1879)**
Age (years)	n=499	n=1353
	Mean 21	Mean 21
	Median 11	Median 11
	Range 1-80	Range 1-89
	<18 years 323 (65%)	<18 years 997 (74%)
Sex	n=539	n=1716
	Male 274	Male 888
	Female 265	Female 828
Initial FDA received date	2008 223	2008 601
	2009 84	2009 258
	2010 59	2010 202
	2011 45	2011 144
	2012 39	2012 174
	2013 101	2013 500
Event Date	n=410	n=1182
	1999 2	1989 1
	2000 1	1992 1
	2002 2	1997 1
	2003 3	1998 7
	2004 2	1999 4
	2005 3	2000 7
	2006 13	2001 7
	2007 47	2002 8
	2008 164	2003 19
	2009 67	2004 33
	2010 37	2005 39
	2011 37	2006 71
	2012 24	2007 155
	2013 8	2008 291
		2009 169
		2010 131
		2011 106
		2012 95
		2013 37
Country of reporter	United States 535	United States 1533
	Foreign 16	Foreign 346

Report type	Expedited 190 Direct 335 Periodic 26	Expedited 1096 Direct 642 Periodic 141
Serious Outcomes*	n=508 Life-threatening 50 Hospitalized 52 Disability 31 Required Intervention 12 Other 363	n=1862 Life-threatening 192 Hospitalized 297 Disability 113 Congenital anomaly 2 Other serious 1258
Frequently reported PTs[‖,‡]	n=551 Abnormal behaviour (159), depression (155), suicidal ideation (145), aggression (143), anxiety (124), anger (91), crying (84), insomnia (73), nightmare (69), mood altered (57), irritability (54)	n=1879 Suicidal ideation (512), depression (464), aggression (357), abnormal behaviour (344), anxiety (324), suicide attempt (254), insomnia (215)
Most frequently reported PTs in reports with a serious outcome [†, ‡]	n=914 reports Depression (132), suicidal ideation (132), aggression (121), abnormal behaviour (120) anxiety (101), anger (71), crying (67), insomnia (59), mood swings (57), nightmare (54)	n=2811 reports Suicidal ideation (465), depression (380), aggression (288), abnormal behaviour (255), anxiety (255), suicide attempt (249), insomnia (178), nightmare (148), agitation (125), irritability (123), mood swings (117), crying (116), anger (112)
Primary suspect medication	Montelukast 546 Other medications 5	Montelukast 1816 Other medications 63
Most frequent indication for montelukast use[§]	n=612 Multiple allergies (223), hypersensitivity (162), seasonal allergy (103), rhinitis allergic (95), rhinitis (16), sinus disorder (13)	n=1190 Asthma (1088), cough (29), bronchial hyperreactivity (25), asthma exercise induced (20), bronchitis (14), COPD (14)
Concomitant medications	Associated with neuropsychiatric events (10)	Associated with neuropsychiatric events (25)

*Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events. Reports may include multiple outcomes.

‖ PTs with ≥ 50 occurrences for allergic indication; ≥ 200 occurrences for asthma indication

† PTs with ≥ 50 occurrences for allergic indication; ≥ 100 occurrences for asthma indication

‡ each report may have multiple PTs

§PTs with ≥ 10 occurrences

3.3 DISCUSSION

The FAERS reports of neuropsychiatric events in Table 6 were mostly from the US. The patients in this report series for allergic and asthma related indications tended to be younger

(median age 11 years) compared to patients in the total FAERS report series (median age 31 years, Table 4). This is consistent with the drug use data that states among the 14.5 million pediatric patients aged 0-17 years old, pediatrics aged 6-14 years old accounted for the majority of patients at approximately 60% of total pediatric patients.

The most frequently reported neuropsychiatric PT when montelukast was used for allergy-related indication was Abnormal behaviour (n=159). Multiple allergies (PT) and Hypersensitivity (PT) were the most frequently reported indications for montelukast use among these patients. Among the 93 reports that provided information on concomitant drugs, only 10 reports stated the patient was taking concurrent medications that were associated with neuropsychiatric adverse events.

The most frequently reported neuropsychiatric PT when montelukast was used for asthma-related indication was suicidal ideation (n=512). There were 63 patients taking montelukast for asthma indication that were taking other suspect medications (predominately allergy medications). There were 25 patients taking concomitant medications that were associated with neuropsychiatric adverse events.

Most of the neuropsychiatric PTs reported are labeled events with the exception of crying. However, crying may be a manifestation of reported PT terms Irritability and Mood swings. Although a mechanism of action for montelukast causing these neuropsychiatric events is unknown at the present time, it was important to convey the findings of FAERS data to the public on two occasions in 2008 and 2009.[2,3] Patients and healthcare providers were advised to monitor for symptoms and to consider discontinuation of the drug in the event of these symptoms occurring.

4 CHURG-STRAUSS SYNDROME

4.1 METHODS AND MATERIALS

4.1.1 FAERS Search Strategy

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 7.

Table 7. FAERS Search Strategy for Churg-Strauss Syndrome*	
Date of search	November 15, 2013
Time period of search	July 16, 2009^ - October 31, 2013
Product Terms	Active Ingredient: Montelukast Montelukast sodium
MedDRA Search Terms	Preferred Tem: Allergic granulomatous angiitis

* See Appendix A for description of the FAERS database.
^ FAERS searched from date of previous review to data lock date for this review.

4.2 RESULTS

The FAERS search retrieved 149 reports. Table 8 summarizes the 149 FAERS reports of Churg-Strauss Syndrome (CSS) reported with montelukast for this report series.

Table 8. Crude Counts* of FAERS Reports of CSS with Montelukast use, received by FDA from July 16, 2009 to October 31, 2013 (N=149)		
Age (n=115)	Mean	51 years
	Median	54 years
	Range	8-81 years
	<18 years	5% (6/115)
Sex	Male	57
	Female	78
	Unknown	14
Report year	2009	24
	2010	30
	2011	26
	2012	31
	2013	38
Country of reporter	United States	49
	Foreign	100
Report type	Expedited	148
	Direct	1
Serious Outcomes^	Death	1
	Life-threatening	15
	Hospitalized	90
	Disability	15
	Other serious	82
Indication	Asthma	106
	Sinusitis	2
	Allergic rhinitis	1
	Bronchitis	1
	Hypersensitivity	1
	Nasal polyp	1
	Obstructive airway	1
	Unknown	36
Concomitant steroid medication^ (n=85)	Inhaled steroid	73
	Oral steroid	25
History of Asthma	Yes	118
	No	4
	Not reported	27

* These reports have not been assess for an association with montelukast and may contain duplicates.

^ Reports may report more than one outcome or steroid medication

4.3 DISCUSSION

The FDA has been aware of the potential association of CSS and montelukast since the montelukast's approval in 1998. In addition, CSS has been included in the montelukast's prescribing information since approval. CSS (also known as eosinophilic granulomatosis with

polyangiitis) is a small and medium sized artery necrotizing vasculitis, most often occurring in patients with adult-onset asthma, allergic rhinitis, nasal polyposis, or a combination, with a mean age of onset of 48 years of age.[16] The American College of Rheumatology has proposed 6 criteria for the diagnosis of CSS, and the presence of 4 or more criteria is usually used for diagnosis. These criteria include: (1) asthma; (2) eosinophilia > 10% in peripheral blood, (3) paranasal sinusitis, (4) pulmonary infiltrates, (5) histological proof of vasculitis with extravascular eosinophils, and (6) mononeuritis multiplex.[17]

Additional reviews of the potential association between CSS and montelukast have been performed since montelukast approval; however, since the underlying pathophysiology of CSS is poorly understood, the mechanism of action of medications to contribute to the development of CSS could not be identified.[4,18] The 2009 FDA response to the Petition acknowledged post-market safety reports and published reports do show a potential association of CSS and montelukast, but causality could not be determined. [4]

Reports of CSS with montelukast use continue to be submitted to FAERS, 149 reports since July 16, 2009. These reports were not further evaluated for an association with montelukast since the potential association of CSS with montelukast is well-documented. However, this review does not indicate any increased trend in severity or frequency of reporting. The current montelukast prescribing information adequately informs healthcare professionals of this potential association. In addition, the montelukast patient information sheet provided with the prescription adequately informs patients, in consumer-friendly language, of CSS. The patient information has a description of CSS, symptoms of CSS, and instructions for patients to contact their healthcare professional immediately if they experience these symptoms (see Appendix B).

In contrast, the proposed OTC Drug Facts label for montelukast does not offer any information for consumers about the potential association with CSS, symptoms of CSS or what to do if symptoms develop. The NDA submission indicates Merck did not include this information on the Drug Facts label since there is insufficient information to establish a causal relationship with montelukast and CSS.

Consideration should be given to include labeling for CSS on the OTC Drug Facts montelukast label because asthmatic patients potentially may use OTC montelukast and CSS can be described in consumer-friendly language as done in the Patient Information section of the prescription montelukast label. In addition, in general, early diagnosis of CSS improves survival. With treatment, the 1-year survival rate for CSS is 90%.[19]

Although the proposed indication for the OTC montelukast does not include asthma, asthma is not contraindicated on the proposed Drug Facts label. The proposed label states, “If you have asthma and allergies, you can use this product for your allergies if you are not taking another drug containing montelukast sodium.” The potential exists that patients with asthma may use OTC montelukast, which increases the importance of including labeling for CSS.

5 CONCLUSION

A review of post-marketing data for montelukast did not identify any new safety issues that have not been previously recognized and reviewed by the FDA. The most often reported safety issues

were related to neuropsychiatric events and Churg-Strauss Syndrome associated with montelukast use. However, there continues to be a lack of well-designed epidemiologic studies that can lead to the quantification of the suicide/suicide attempt risk level among patients using montelukast.

The neuropsychiatric events appear to be adequately labeled in the proposed OTC montelukast Drug Facts label submitted with NDA 204804; however, the proposed OTC montelukast Drug Facts label lacks information about the potential association between montelukast use and Churg-Strauss Syndrome.

6 RECOMMENDATIONS

Although approvability of an OTC montelukast product is beyond the scope of this review, DPV agrees with the proposed labeling for neuropsychiatric events on the OTC montelukast Drug Facts label submitted with NDA 204804, but the Drug Facts label lacks information about CSS.

Therefore, DPV recommends the following for consideration:

- If approved, add a statement to the OTC montelukast Drug Facts label Warnings Section and Consumer Leaflet for Churg-Strauss Syndrome using language that is similar to language found in the prescription montelukast Patient Information.
- Potential OTC labeling for Churg-Strauss Syndrome:
  Stop Use and ask your doctor if:
    - you start to have pain in your joints
    - you have a feeling of pins and needles or numbness of arms or legs
    - you develop red-purple dots on the skin that look like a rash or bruise

    Sometimes people with asthma may develop a condition that makes their blood vessels become inflamed throughout their body (systemic vasculitis) when taking SINGULAIR Allergy. This sometimes happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.

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8 APPENDICES

8.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FDA implemented FAERS on September 10, 2012, and migrated all the data from the previous reporting system (AERS) to FAERS. Differences may exist when comparing case counts in AERS and FAERS. FDA validated and recoded product information as the AERS reports were migrated to FAERS. In addition, FDA implemented new search functionality based on the date FDA initially received the case to more accurately portray the follow up cases that have multiple receive dates.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

Data Mining of FAERS using Empirica Signal

Empirica Signal refers to the software that OSE uses to perform data mining analyses while using the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm. "Data mining" refers to the use of computer algorithms to identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. These potential signals can then be evaluated for intervention as appropriate. In OSE, the FDA Adverse Event Reporting System (FAERS) database is utilized for data mining. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in FAERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data. Further, drug and event causality cannot be inferred from EBGM scores.

8.2 APPENDIX B. SELECTED SECTIONS OF THE SINGULAIR PATIENT INFORMATION

What are the possible side effects of SINGULAIR?
SINGULAIR may cause serious side effects.

- **Behavior and mood-related changes.** Tell your healthcare provider right away if you or your child have any of these symptoms while taking SINGULAIR:

• agitation including aggressive behavior or hostility • attention problems • bad or vivid dreams • depression • disorientation (confusion) • feeling anxious • hallucinations (seeing or hearing things that are not really there)	• irritability • memory problems • restlessness • sleep walking • suicidal thoughts and actions (including suicide) • tremor • trouble sleeping

- **Increase in certain white blood cells (eosinophils) and possible inflamed blood vessels throughout the body (systemic vasculitis).** Rarely, this can happen in people with asthma who take SINGULAIR. This sometimes happens in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered.
  Tell your healthcare provider right away if you get one or more of these symptoms:
  - a feeling of pins and needles or numbness of arms or legs
  - a flu-like illness
  - rash
  - severe inflammation (pain and swelling) of the sinuses (sinusitis)

The most common side effects with SINGULAIR include:

- upper respiratory infection
- fever
- headache
- sore throat
- cough
- stomach pain
- diarrhea
- earache or ear infection
- flu
- runny nose
- sinus infection

8.3 APPENDIX C. LINE LISTING OF UNIQUE COMPLETED SUICIDE FAERS REPORTS[d] FROM JUNE 13, 2008 TO OCTOBER 31, 2013 (N=43)

	FAERS Case #	MFR control #	FDA Initial Received Date	All Suspect Products	All Preferred Terms	Age (Years)	Sex	Montelukast Indication	Concomitants	Reporter Country
	Summary of Case Narrative									
1)	6669700	US-MERCK-0806USA02726	6/17/2008	Singulair	Completed suicide	14	F	Not reported	None reported	USA
	A physician reported a 14 year old received montelukast (unknown dose, duration, indication). She committed suicide at an unknown time. Upon follow-up, the physician did not think the suicide was related to montelukast. No other information reported.									
2)	6672403	ES-MERCK-0806ESP00020	6/19/2008	Singulair	Completed suicide	73	M	Chronic Obstructive Pulmonary Disease	Acetylcysteine; Fluticasone/ Salmeterol; Ipratropium	Foreign
	A physician reported a 73 year old male with chronic alcohol abuse (not excessive) and "domestic psychological abuse" received montelukast 10 mg once daily from Dec 15, 2003. On March 15, 2008, the patient committed suicide by hanging. The physician indicated the patient was mildly obsessive, occasionally presented with "mood disturbances," but never required psychiatric intervention nor drug treatment (antidepressants) for these issues. A few hours before the patient's suicide, the patient suffered a "familiar incident," became intoxicated, and then was not allowed to attend his grandson's baptism due to the intoxication. No other information reported.									
3)	6717135	US-MERCK-0807USA04321	8/1/2008	Singulair	Completed suicide; Headache; Suicidal ideation; Suicide	15	F	Allergic Rhinitis; Asthma	Synthroid	USA
	A physician reported a 15 year old white female began using montelukast "about 10 years ago" (approximately January 1999), first using 5 mg tablets (unknown daily dose and indication). She was switched to montelukast 10 mg tablets once daily on approximately July 2002. She was evaluated by a pulmonologist in 2002 and diagnosed with mild asthma, prescribed albuterol, fluticasone propionate, and Rhinocort for post-nasal drip, but was reportedly non-compliant. The physician next saw the patient in 2007, when she presented with chronic cough and some episodes of sinusitis. The physician reported that she was experiencing suicidal thoughts, and attempted suicide in approximately July 2007, which resulted in a hospitalization. In December 2007, the patient was restarted on montelukast 10 mg once daily for the treatment of both upper and lower airway inflammation, asthma and allergic rhinitis (duration not reported). A 2nd suicide attempt was reported in "early 2008" (approximately March or April), when she jumped off a bridge into water. She was treated at an inpatient psychiatric facility for a few weeks and was briefly on antidepressants. In approximately April 2008, therapy with montelukast was discontinued. The patient was seen in May 2008, at which time she was on estradiol and Synthroid for hypothyroidism. Allergy									

[d] Duplicate reports have been removed from this table. These reports have not been evaluated for an association between completed suicide and montelukast use.

	immunotherapy was started in June 2008 through December 2008. She frequently complained of frontal headaches, but was never found to have bacterial sinusitis. She was advised to irrigate her nose with normal saline solution. On 13-JAN-2009, the patient had committed suicide after jumping in front of a train. Autopsy is pending. The reporter felt that the patient's suicidal thoughts were not related to therapy with montelukast.									
4)	6721354	US-MERCK-0808USA00349	8/7/2008	Singulair	Completed suicide; Depression; Sleep disorder; Social avoidant behaviour	17	M	Not Reported	None Reported	USA
	Received from a Singulair BLOG posting on the internet provided by Hill and Knowlton Public Relations Agency on 31-JUL-2008. The posting dated 09-APR-2008 stated the following: "My son started taking Singulair at the age of 13 after Claritin became an over the counter drug. Over the years he started to have sleeping problems and was dealing with depression on a regular basis. We went to the doctors for help and were prescribed drugs for depression which he said didn't help. He started to isolate himself from family events, dropped out of high school and started sleeping a few hours during the day because he said he couldn't sleep at night. On the morning on January 4th of 2006, I was informed by the local police Dept, after I reported my son missing, that he had "passed on". They had found him in his car with his hunting rifle between his legs." No further information is expected due to limited source details reported in the BLOG.									
5)	6721375	US-MERCK-0808USA00352	8/7/2008	Singulair	Completed suicide	N/A	F	Not Reported	None Reported	USA
	Information has been received from a Singulair BLOG posting on the internet provided by Hill and Knowlton Public Relations Agency on 31-JUL-2008. The posting dated 28-MAR-2008 stated the following: "My mother was on Singulair for at least 2 years, she committed suicide April 1, 2006." No further information is expected due to limited source details reported in the BLOG.									
6)	6752575	Not Applicable	9/3/2008	Singulair	Completed suicide; Osteoporosis; Personality change; Spinal fracture; Thermal burn	41	M	Asthma	Percocet	USA
	A wife reported her husband received prednisolone and singulair after being diagnosed with chronic asthma in 2001. He required multiple hospitalizations. He was hospitalized from May to Sept. 20, 2004, a consequence of a drug-induced side effect, that included osteoporosis, which caused a fracture in his spine and required surgery between Oct. and Dec. 2004 in the U.S. Upon return from the U.S., his asthma improved. He was still on singulair plus Percocet for pain. He also received monthly treatment for osteoporosis (unknown medication) for a year and half. During that time, his attitude changed "continuously." On July 12, 2006, he attempted suicide by setting himself on fire with gasoline. As a result, he had burns over 70% of his body. He died 4 days later.									
7)	6753899	US-MERCK-0809USA01237	9/11/2008	Singulair	Completed suicide; Gun shot wound	56	F	Asthma	Albuterol	USA

	A nurse reported her 56 year old sister, who had a pertinent medical history for asthma, allergies and no known drug allergy, was placed on therapy with montelukast for asthma (dose and duration not reported). The nurse could give no details regarding dates of montelukast use, but believed her sister had taken it for a "long time". Concomitant medication included "asthma inhalers" including as needed albuterol. It was reported that on 17-FEB-2005 the patient committed suicide by shooting herself during the course of montelukast sodium therapy. No further information is available.									
8)	6766214	FR-MERCK-0809FRA00042	9/22/2008	Fluticasone/ Salmeterol; Singulair	Completed suicide; Intentional overdose	17	M	Asthma	Fluticasone	Foreign
	A physician reported a 17 year old male patient was placed on montelukast 10 mg once a day for asthma in 2003. Concomitant therapy included fluticasone propionate 2 puffs daily started in 2002 for asthma. In Feb 2008, the patient and his family moved from France to Romania. There was no medical history of depression or anxiety or behaviour disorder. In April 2008, in the afternoon, the patient said that he was tired and he went to his bedroom for sleeping. By the end of the afternoon, the patient's father found his son dead (cyanosis+). The patient committed suicide by using 3 boxes of montelukast sodium (840 mg) and one box of fluticasone/salmeterol (diskus) and other drugs (no specified). The patient explained in a letter that he was tired and he was fed of the life. Autopsy was performed and did not show any specific anomalies. The cause of death was completed suicide with therapies overdose. The reporting physician felt that intentional overdose was related to therapy with montelukast sodium and fluticasone/salmeterol.									
9)	6801437	US-MERCK-0810USA05003	10/31/2008	Singulair	Completed suicide	N/A	N/A	Not reported	None reported	USA
	A physician stated a patient's mother heard that a child in her neighborhood was placed on therapy with montelukast sodium, chewable tablet for two weeks (dose and indication not reported) and committed suicide. Attempts are being made to verify the existence of an identifiable patient and reporter. Attempts to verify the existence of an identifiable patient have been unsuccessful.									
10)	6890741	Not Applicable	1/15/2009	Singulair	Completed suicide; Lung neoplasm malignant	77	M	Asthma	None reported	USA
	I saw a new clip on Fox news network about the drug singulair, that it could possibly cause suicidal tendencies. My father committed suicide on 2/10/08 after being diagnosed with lung cancer. I did see one prescription that he had for singulair after going through some of his prescriptions. I am not sure how much he used. He did have a long history of asthma and used prescription medicines for a long time. Again I'm not sure how much of this drug he used. Just wanted to make a report.									
11)	6891211	Not Applicable	1/16/209	Singulair	Completed suicide	76	M	Chronic Obstructive Pulmonary Disease	None reported	USA
	A wife reported her husband had been on Singulair 10 mg for 3 years or longer for chronic obstructive pulmonary disease. He had been in the hospital three times between Dec. 2007 and March 2008 (unknown cause for hospitalization). He was released from the hospital on Sunday, March 9th. He took his life on Monday afternoon. There was no note or explanation left by him before he committed suicide. They were happily married for fifty years. No other information was reported.									
12)	6900030	Not Applicable	1/26/2009	Singulair	Anxiety; Completed Suicide; Depression;	21	M	Multiple allergies; asthma	Flonase; Intal inhaler; Proventil	USA

					Mood altered					
	A mother reported her son had taken Singulair for about 6 years at the time of his death. In his suicide letter he states he had felt depressed, anxious for several years and could not take it any longer. No other information reported.									
13)	6902205	GB-MERCK-0901GBR00090	2/5/2009	Singulair	Completed suicide	61	F	Not reported	None reported	Foreign
	A physician who authored a literature article, (Jick, Wilcox, Hagberg, Egger. Rate of suicide in patients taking montelukast. Pharmacotherapy. 2009;2(29):165-166.) reported a 61 year old female with asthma (for the past 29 years) and depression (for the past 10 years) was placed on montelukast (dose, duration and indication not reported). Subsequently the patient committed suicide. The literature stated, "She was prescribed one 28 day prescription for montelukast sodium approximately two years before her death". The physician felt that the suicide was not related to therapy with montelukast sodium. The literature article also stated, "Based on the timing of the prescription and her pertinent medical history, we determined that montelukast sodium could not have been the cause of the suicide". No further information is available.									
14)	7000825	Not Applicable	5/13/2009	Singulair	Completed suicide	50	M	Asthma	None reported	USA
	A consumer reported a patient committed suicide. No other information reported.									
15)	7006891	US-MERCK-0905USA03621	5/29/2009	Singulair	Completed suicide	N/A	N/A	Not reported	None reported	USA
	A consumer reported a patient received montelukast (dose, duration and indication not reported). In January 2009, the patient died by suicide. No further information is available.									
16)	7010036	US-MERCK-0905USA03623	6/3/2009	Singulair	Completed suicide	14	M	Not reported	None reported	USA
	A consumer reported a 14 year old male received montelukast (dose, duration and indication not reported). In February 2008, the patient died by suicide. No further information is available.									
17)	7015118	US-MERCK-0906USA00972	6/9/2009	Singulair	Completed suicide	7	F	Asthma	Albuterol	USA
	A physician reported a 7 year old black female received montelukast 5 mg chewable tablet, (duration and indication not reported) for asthma. She had a history of pneumonia and no known drug allergies. Montelukast was prescribed in September 2003 and June 2006 (doses not indicated) but stopped by family both times (stop dates unknown), concomitant medication included: albuterol. She restarted montelukast 5 mg once daily on July 27, 2007, due to flair up of asthma symptoms. The patient was last seen in the office in August 2007. In approximately 2008 "about a year ago", the patient committed suicide and was found with a belt around her neck. The physician reported that he was not sure if montelukast sodium was attributed to the suicide and stated that the patient was not depressed. The physician heard about the event from the Hasbro Hospital ER in Providence, RI. The ER indicated the patient had been watching a violent show on television. The date of death was 20-FEB-2008. This case was investigated by Child Protective Services.									
18)	7025974	US-MERCK-0906USA02512	6/17/2009	Singulair	Completed suicide	N/A	N/A	Not reported	None reported	USA
	A consumer heard on a news channel that a patient committed suicidal on January 14, 2009, while on montelukast and montelukast made him suicidal.									
19)	7029695	US-MERCK-0906USA02982	6/22/2009	Singulair	Asphyxia; Chest pain; Completed suicide; Decreased appetite; Foot	58	M	Asthma	Advair; Aspirin; Cipro; Flonase; Lipitor; Nexium; Norvasc; Vytorin	USA

					fracture; Influenza; Nocturia; Respiratory rate decreased; Weight decreased					
	A physician and a medical assistant reported a 62 year old male ex-smoker (stopped in 1974) with no known drug allergies and with asthma, rhinitis allergic, gastro esophageal reflux disease, sleep apnea, periodic limb movement disorder, hypercholesterolemia and hypertension and a history of nasal polypectomy, appendectomy, tonsillectomy, coronary artery bypass graft three times in 2000 and a benign tumor removed from left knee received montelukast 10 mg once daily starting May 4, 2005, for asthma (duration not reported). Concomitant therapy included ciprofloxacin, esomeprazole, aspirin, fluticasone/salmeterol, fluticasone propionate, ezetimibe/simvastatin and amlodipine. On May 3, 2009, the patient committed suicide. The physician stated that the patient had no history of depression. The family declined an autopsy and the remains were cremated. Medical records were obtained.									
20)	7031467	US-MERCK-0906USA03426	6/23/2009	Singulair	Completed suicide	N/A	N/A	Asthma	Unspecified medications	USA
	A physician reported a patient with "many issues" was placed on montelukast on an unspecified date for asthma (dose and duration not reported). The patient was taking other unspecified medications concomitantly. It was reported that "about four years ago", approximately in 2005, the patient committed suicide while taking montelukast. The patient sought unspecified medical attention. No other information reported.									
21)	7067859	US-MERCK-0907USA04598	6/23/2009	Singulair	Completed suicide	11	M	Asthma	None reported	USA
	A physician reported an 11 year old male received montelukast (dose and duration not reported) from an unspecified date for asthma. He suffered from depression “from kids picking on him.” Approximately "2 years ago" on 26-JUL-2007 the patient committed suicide and died. The physician did not feel there was any correlation with montelukast and did not want to file a report. No further information is available.									
22)	7110089	US-MERCK-0909USA00472	9/10/2009	Singulair	Completed suicide	55	M	Not reported	None reported	USA
	A physician reported a male in his late 50s received montelukast 10 mg once daily (duration and indication not reported). The patient committed suicide while taking montelukast. The physician thought it was important to note that he believed "there were some other things going on with this patient unrelated to his medication." A call was placed to the company rep that had a conversation with the physician, and the rep reported that in her conversation with the physician, he had mentioned that he had suggested the deceased’s wife start on montelukast. The widow broke down and told the physician the story about her husband's suicide while on montelukast. No other information reported.									
23)	7250304	US-MERCK-1001USA01447	1/20/2010	Singulair	Adverse event; Anxiety; Completed suicide; Depression	N/A	N/A	Not reported	None reported	USA
	A parent group reported their children were treated with montelukast for unknown indication. The parents reported serious concerns based on their own children's adverse experiences with montelukast. On an unspecified date, their children suffered from physical symptoms and psychiatric disorders,									

	including anxiety, depression which manifested while taking montelukast. The children that did not complete suicide experienced a remission of symptoms when treatment with montelukast sodium was discontinued. Upon internal review (by Merck), the adverse event “suicidal ideation” should read “completed suicide.” No other information received.									
24)	7252790	US-MERCK-1001USA01446	1/22/2010	Singulair	Adverse event; Anxiety; Completed suicide; Depression	N/A	N/A	Not reported	None reported	USA
	A parent group reported their children were treated with montelukast for unknown indication. The parents reported serious concerns based on their own children's adverse experiences with montelukast. On an unspecified date, their children suffered from physical symptoms and psychiatric disorders, including anxiety, depression which manifested while taking montelukast. The children that did not complete suicide experienced a remission of symptoms when treatment with montelukast sodium was discontinued. Upon internal review (by Merck), the adverse event “suicidal ideation” should read “completed suicide.” No other information received.									
25)	7304308	US-MERCK-1002USA04084	3/3/2010	Singulair	Completed suicide	N/A	M	Not reported	None reported	USA
	It was reported by a news station that "about two years ago” a male patient while taking montelukast sodium, for an unspecified reason, had “committed suicide" and died. The cause of death was suicide. The news station today (26-FEB-2010) was doing a follow up report regarding the parents of the child who was taking montelukast sodium and committed suicide. The report stated that they were going to lobby about restrictions for medication labels.									
26)	7321204	Not Applicable	2/25/2010	Montelukast	Completed suicide; Depression; Gun shot wound	62	M	Nasopharyngitis; Multiple allergies	None reported	USA
	Patient committed suicide by gun shot wound. He had been on montelukast prior to VA care > 2 yrs. prior to suicide. He had a history of depression.									
27)	7327169	US-MERCK-1003USA02053	3/22/2010	Singulair	Abnormal dreams; Appendix disorder; Completed suicide; Oro-pharyngeal pain	15	M	Asthma; Allergic rhinitis	Astelin; Claritin	USA
	A physician reported a 15 year old male patient with no history of mental illness who in 2000 was placed on montelukast 5 mg once daily but intermittently for the treatment of rhinitis allergic and asthma. He was last hospitalized for asthma 10 years ago (in 2000). Concomitant therapy included loratadine and azelastine hydrochloride. He was switched to montelukast 10 mg once daily when he turned 15 years of age on November 7, 2009. The patient's insurance did not cover the medication and it took almost two months before it was approved from the insurance company. He did not use montelukast during this time. On February 22, 2010, he started taking montelukast 10 mg tablet once daily, and he was taking the 10 mg tablet for 5 days before he committed suicide and died on February 27, 2010. The physician stated he died of either a large ingestion of acetaminophen or a "horrific stab to the chest". A suicide note was found. Additional information, the patient was placed on antidepressants on an unspecified date.									

28)	7365549	Not Applicable	4/16/2010	Singulair	Asphyxia; Completed suicide	51	M	Angioedema	None reported	Foreign
	The patient committed suicide by hanging on March 20, 2010 while taking Singulair 10 mg once daily. No other information reported.									
29)	7547180	US-MERCK-1008USA00975	8/19/2010	Singulair	Completed suicide; Overdose	N/A	M	Not reported	None reported	USA
	A physician reported a male patient was placed on montelukast 10 mg (duration and indication not reported) in December 2009. It was reported that in June 2010, the patient committed suicide 6 months after starting therapy with montelukast, the patient died due to an illegal drug overdose. The physician believed that the patient's death was unintentional and had nothing to do with montelukast sodium. He refused to give the patient's date of death, and was not sure when the patient's last dose of montelukast was as the last prescribed refill was a while ago (date not reported).									
30)†	7742156/ 7744612	CA-MERCK-1012USA03456 & CA-MERCK-1012USA03457	12/28/2010	Singulair	Completed suicide	51	M	Hypersensitivity; Asthma	Cetirizine; Lipitor	Foreign
	Information has been received from a foreign agency concerning a 51 year old male patient who received montelukast 10 mg once a day for asthma and allergies (duration and start date not reported). Concomitant medications included: atorvastatin (LIPITOR) fore elevated cholesterol and cetirizine (REACTINE) for episodic angioedema. The patient completed suicide on an unreported date in 2010. The patient had no prior mental health problems, was very happy and had plans. There were no changes noted by the family or friends prior to the suicide. There was no interaction with other suspected drug. No further information is available. This was originally reported by a consumer. The agency considered that completed suicide and therapy with montelukast sodium were related.									
31)	7844740	US-MERCK-1103USA00462	3/7/2011	Singulair	Completed suicide	22	M	Not reported	None reported	USA
	A nurse practitioner reported a 22 year old male received montelukast (dose, duration and indication not reported). On approximately 02-JUL-2010 ("8 month ago"), the patient committed suicide and died. The patient did not seek medical attention. No further information is available.									
32)	8070128	US-MERCK-1107USA04085	8/4/2011	Singulair	Completed suicide	13	M	Asthma	Advair Diskus	USA
	A physician reported a 13 year old male received montelukast for asthma beginning in approximately 2001 (dose and duration not reported). Concomitant therapy included fluticasone/salmeterol (ADVAIR). On February 4, 2010, the patient committed suicide and died. The physician further stated that he "was not seeing the patient at the time of the suicide because the family had moved out of the area" and there was also a divorce that was occurring at the time of the suicide. No other information reported.									
33)	8312796	US-MERCK-1112USA03077	12/27/2011	Singulair	Completed suicide; Depression; Suicidal ideation	N/A	M	Not reported	None reported	USA
	A physician reported a male "over 12 years old" received montelukast 10 mg once daily "for a long time" (duration and indication not reported). The patient experienced severe depression, suicidal thoughts on an unspecified date. The patient had sought unspecified medical attention. No treatment was given for the adverse effects. The patient committed suicide in December 2011. No other information reported.									
34)*	9003095	US-009507513-	1/8/2013	Acetaminophen;	Cardio-	54	F	Not reported	None reported	USA

		1301USA002065		Singulair; Duloxetine; Fenofibrate; Fluoxetine; Flurazepam	respiratory arrest; Completed suicide					
	This report has been received by Merck from a line listing from the AERS Database. This spontaneous report refers to a 54 years old female patient. The patient started therapy with montelukast (dose, duration, and indication not reported). Other suspect therapies included fenofibrate, fluoxetine, duloxetine, acetaminophen, and flurazepam. No other medications were reported. On an unknown date the patient experienced death by completed suicide and cardio-respiratory arrest. No details for death are available.									
35)*	9007813	US-009507513-1012USA00493	1/11/2013	Advair; Singulair	Asphyxia; Completed suicide	50	F	Asthma	Levothryroxine; Potassium	USA
	This report was received by Merck from a Freedom of Information request to the FDA. A consumer reported a 50 year old female patient had been prescribed and was using both montelukast (dose not reported) and fluticasone/salmeterol (ADVAIR) (diskus) to treat asthma starting in March 2009. "She also battled anorexia nervosa for many years. She committed suicide by hanging on December 6, 2009. She had never previously indicated any thoughts or intentions of suicide and was a practicing Catholic who raised their children in the same religion. She left behind their three beautiful children ages 11, 13 and 15. She was Christmas shopping that day with the reporter and their son. She had already bought gifts for the family. She was planning Christmas dinner and for their 11 year old daughter's birthday -Christmas day as well-. She had been taking these medications for approximately 9 months to one year."									
36)*	9010584	US-009507513-0812USA00678	1/9/2013	Singulair	Completed suicide	16	M	Hypersensitivity; Asthma	Advair; Albuterol	USA
	This report was received by Merck from a Freedom of Information request to the FDA. On October 13, 2003, a 16 year old male patient was placed on montelukast 10 mg once daily (also reported as 10 mg daily as needed), for the treatment of allergies and asthma. Concomitant therapies included fluticasone/salmeterol (ADVAIR DISKUS) and albuterol, as needed when exercising. The patient usually exhibited asthma symptoms with strenuous exercise. The patient was a healthy, active and involved student in high school. The patient had his annual physical on an unspecified date (result unknown) where the physician noted the adolescent as well. The last prescription of montelukast was filled on April 17, 2006. On August 22, 2006, the patient died by suicide after taking montelukast for approximately 3 years.									
37)	9011809	US-009507513-1301USA003708	1/13/2013	Acetaminophen; Androgen receptor antagonist; Prinivil; Quetiapine fumarate; Salicylate meglumine; Singulair; Prochlorperazine	Completed suicide	61	F	Not reported	None reported	USA
	A health professional reported a 61 year old female patient received montelukast (unknown dose, duration, and indication) along with other suspect therapies which include androgen receptor antagonist, prochlorperazine, lisinopril, salicylate meglumine, quetiapine fumarate, and acetaminophen. On an									

	unknown date the patient committed suicide and died. No details for death are available.									
38)*	9012701	US-009507513-1301USA002757	1/14/2013	Singulair	Bipolar disorder; Completed suicide; Gun shot wound; Personality change	17	M	Asthma	None reported	USA
	This report has been received by Merck from the AERS Database. This spontaneous report refers to a 17 years old male patient who received montelukast for asthma (dose and duration not reported). No other medications were reported. On an unknown date, the patient experienced bipolar disorder, personality change, committed suicide and died. No details for death are available.									
39)	9107341	US-009507513-1302USA009793	2/21/2013	Singulair	Completed suicide; Depression	N/A	M	Hypersensitivity	Advair; Spiriva	USA
	A wife reported her husband (age not reported) received montelukast 10 mg (unknown frequency) for allergies beginning on July 23, 2010. Her husband was not suicidal at the time he started using montelukast, but became "very depressed" while on montelukast therapy. The concomitant therapies he received included fluticasone/salmeterol (ADVAIR) and tiotropium bromide (SPIRIVA). He committed suicide in November 2012 and died. No other information reported.									
40)	9108560	US-009507513-1302USA008908	2/22/2013	Singulair	Abnormal behavior; Completed suicide; Irritability; Mood altered; Personality change; Poor quality sleep	12	F	Rhinitis allergic; Asthma	Advair; Dulera; Symbicort	USA
	A physician assistant reported a 12 year old white female patient received montelukast 5 mg (frequency not reported) beginning on an unknown date in 2009. The patient's past medical history included asthma and allergic rhinitis but with no history of depression. On an unknown date in 2012, the patient switched to generic montelukast from brand Singulair. Beginning in September 2012, the patient experienced a change in mood, becoming irritable, moody, had trouble sleeping and developed a "bad attitude." The patient was seen by the physician assistant on December 20, 2012 and the behavioral changes were reported by the patient's mother. Montelukast was discontinued, but the behavioral changes did not abate after stopping the drug. It was noted that the patient's compliance with montelukast was "low." The concomitant medications included: ADVAIR (250 Microgram) twice daily from 16-OCT-2012 to 10-NOV-2012 for asthma, SYMBICORT (160 Microgram) twice daily from 20-NOV-2012 to 20-DEC-2012 for asthma and DULERA (100/5 microgram) 2 puffs twice a day from 20-NOV-2012 for asthma. On February 11, 2013, the patient committed suicide. No other information reported.									
41)	9198384	Not Applicable	3/27/2013	Montelukast	Completed suicide	48	M	Asthma	Advair Diskus; Spiriva Handihaler	USA
	Suicide with handgun. No other information reported.									

42)	9356213	US-MERCK-1306USA007331	6/19/2013	Singulair	Completed suicide; Depression; Mental disorder; Thinking abnormal	N/A	M	Asthma	Advair; Spiriva	USA
	A consumer reported her husband of unknown age received montelukast 10 mg once daily for asthma since approximately April 2011 ("prescribed to him over two years"). He had a past medical history of chronic obstructive pulmonary disease, alcohol use (rare) and smoker who quit on July 11, 2010. His concomitant therapies included: Advair Diskus 500/50 mg and Spiriva handihaler capsule 18mcg. On an unknown date, he "turned into a very depressed man." On November 16, 2012, he committed suicide with a handgun. No other information reported.									
43)	9636214	NSR_01298_2013	10/17/2013	Domperidone; Montelukast; Tramadol; Tranexamic acid	Completed suicide; Convulsion; Drug interaction; Hypoglycemia	36	N/A	Not reported	None reported	Foreign
	Citation(s): Abadie D. Durrieu G. Roussin A. Montastruc JL. le Reseau Francais des Centres Regionaux de Pharmacovigilance. ("Serious" adverse drug reactions with tramadol: a 2010-2011 pharmacovigilance survey in France]. Therapie 2013;68(2):77-84. Description of Event or Problem: It was reported in scientific literature by health professionals from France in a retrospective study of serious adverse effects from companies selling medications containing tramadol a 36 year old patient (unknown gender), with unknown history, ingested massive amounts of tramadol (unknown quantity), along with tranexamic acid, montelukast, and domperidone. The patient experienced hypoglycemia with seizures. The patient ingested the drugs in a reported suicide attempt, which resulted in death. No other information reported.									

†This line contains a report and its duplicate report. Both reports were used to gather the information in the line listing.

* These reports were gathered by Merck through Freedom of Information requests to the FDA or the public AERS database. They may include duplicates cases that were reported in the 2008 OSE review of montelukast and completed suicides.

8.4 APPENDIX D. AUDIT TRAILS FOR ASTHMA AND ALLERGY INDICATION PTS

Asthma indication PTs:

Case Series Name: Copy of 4610 Montelukast asthma indic and psych soc [551 cases]
Query Logic:
Return cases based on the following conditions and on the selection logic: (((((1 intersect 2 intersect 3 intersect 8) minus 4) minus 5) minus 6) minus 7)
1) Generic name equals 'Montelukast'
2) PT equals any of the following values: 'Feeling of despair', 'Abnormal dreams', 'Fear', 'Panic disorder', 'Affective disorder', 'Self esteem decreased', 'Self-injurious ideation', 'Nightmare', 'Sleep terror', 'Mood swings', 'Thinking abnormal', 'Anger', 'Depression', 'Suicidal ideation', 'Violence-related symptom', 'Mood altered', 'Depressed mood', 'Anxiety', 'Oppositional defiant disorder', 'Aggression', 'Bipolar disorder', 'Panic attack', 'Screaming', 'Abnormal behaviour', 'Irritability', 'Crying', 'Morbid thoughts', 'Somnambulism', 'Negative thoughts', 'Emotional disorder', 'Self injurious behaviour', 'Mental disorder', 'Bruxism', 'Disturbance in attention', 'Insomnia', 'Suicide attempt', 'Frustration', 'Personality change', 'Intentional self-injury', 'Poor quality sleep', 'Enuresis', 'Affect lability', 'Stress', 'Sleep disorder', 'Decreased interest', 'Paranoia', 'Homicidal ideation', 'Attention deficit/hyperactivity disorder', 'Agitation', 'Social avoidant behaviour', 'Restlessness', 'Sleep talking', 'Tic', 'Initial insomnia', 'Middle insomnia', 'Obsessive thoughts', 'Obsessive-compulsive disorder', 'Hallucination', 'Suicidal behaviour', 'Amnesia', 'Completed suicide', 'Apathy', 'Hypersomnia', 'Autism', 'Hallucination', 'visual', 'Nervousness', 'Psychomotor hyperactivity', 'Somnolence'
3) Indication PT equals any of the following values: 'Food allergy', 'Hypersensitivity', 'Multiple allergies', 'Rhinitis', 'Rhinitis allergic', 'Seasonal allergy', 'Sinus disorder'
4) Indication PT equals any of the following values: 'Asthma', 'Asthma exercise induced', 'Asthma prophylaxis', 'Bronchial hyperreactivity', 'Bronchitis', 'Cough', 'Depression', 'Sinusitis', 'Wheezing' (or is null)
5) Generic name equals any of the following values: 'Albuterol', 'Albuterol And Ipratropium', 'Budesonide And Formoterol', 'Cromoglicic Acid', 'Fluticasone And Salmeterol', 'Formoterol', 'Formoterol And Mometasone', 'Ipratropium', 'Levalbuterol', 'Nedocromil', 'Omalizumab', 'Pirbuterol', 'Salmeterol', 'Theophylline', 'Zafirlukast', 'Zileuton'
6) PT equals any of the following values: 'Completed suicide', 'Death'
7) Outcome died equals 'YES'
8) FDA date is between '03/27/2008' and '10/31/2013', inclusive

Allergy indication PTs:

Case Series Name: Copy of 4610 Montelukast asthma indic and psyc soc [1879 cases]
Query Logic:
Return cases based on the following conditions and on the selection logic: ((((1 intersect 2 intersect 4 intersect 7) minus 3) minus 5) minus 6)
1) Generic name equals 'Montelukast'
2) PT equals any of the following values: 'Abnormal behaviour', 'Abnormal dreams', 'Affective disorder', 'Aggression', 'Agitation', 'Agoraphobia', 'Akathisia', 'Anger', 'Anhedonia', 'Anxiety', 'Anxiety disorder', 'Aphonia', 'Attention deficit/hyperactivity disorder', 'Bipolar disorder', 'Completed suicide', 'Conversion disorder', 'Crying', 'Decreased activity', 'Decreased interest', 'Depressed mood', 'Depression', 'Disturbance in attention', 'Dysphonia', 'Emotional disorder', 'Enuresis', 'Fear', 'Fear of death', 'Feeling guilty', 'Feeling of despair', 'Frustration', 'Hallucination', 'Hallucination, visual', 'Homicidal ideation', 'Initial insomnia', 'Insomnia', 'Intentional self-injury', 'Irritability', 'Major depression', 'Mental disorder', 'Mental impairment', 'Middle insomnia', 'Mood altered', 'Mood swings',

'Morbid thoughts', 'Negative thoughts', 'Nervousness', 'Nightmare', 'Obsessive thoughts', 'Obsessive-compulsive disorder', 'Oppositional defiant disorder', 'Panic attack', 'Panic disorder', 'Paranoia', 'Parasomnia', 'Personality change', 'Poor quality sleep', 'Psychiatric symptom', 'Restlessness', 'Screaming', 'Self esteem decreased', 'Self injurious behaviour', 'Self-injurious ideation', 'Sleep disorder', 'Sleep terror', 'Social avoidant behaviour', 'Social phobia', 'Somnambulism', 'Stress', 'Suicidal behaviour', 'Suicidal ideation', 'Suicide attempt', 'Thinking abnormal', 'Violence-related symptom'
3) Indication PT equals any of the following values: 'Food allergy', 'Hypersensitivity', 'Multiple allergies', 'Rhinitis', 'Rhinitis allergic', 'Seasonal allergy', 'Sinus disorder'
4) Indication PT equals any of the following values: 'Asthma', 'Asthma exercise induced', 'Asthma prophylaxis', 'Bronchial hyperreactivity', 'Bronchitis', 'Cough', 'Sinusitis', 'Wheezing' (or is null)
5) PT equals any of the following values: 'Completed suicide', 'Death'
6) Outcome died equals 'YES'
7) FDA date is between '03/27/2008' and '10/31/2013', inclusive

8.5 APPENDIX E. EMPIRICA SIGNAL DATAMINING RESULTS

Table 9. Data Mining Results with EB05 ≥ 2 for montelukast, by MedDRA Preferred Terms (sorted by Descending EB05 Scores) from approval to October 31, 2013

Generic name	Preferred Term	High Level Term	High Level Group Term	System Organ Class	N	EBGM	EB05
Montelukast	Allergic granulomatous angiitis	Vasculitides	Immune disorders NEC	Immun	841	266.212	251.45
Montelukast	Mononeuritis	Mononeuropathies	Peripheral neuropathies	Nerv	28	69.386	50.216
Montelukast	Pancoast's syndrome	Peripheral neuropathies NEC	Peripheral neuropathies	Nerv	5	110.452	48.149
Montelukast	Hypereosinophilic syndrome	Eosinophilic disorders	White blood cell disorders	Blood	14	75.226	47.164
Montelukast	Allergic respiratory disease	Respiratory tract disorders NEC	Respiratory disorders NEC	Resp	5	58.075	23.439
Montelukast	Eosinophilic myocarditis	Noninfectious myocarditis	Myocardial disorders	Card	13	33.269	20.436
Montelukast	Eosinophilic pneumonia	Lower respiratory tract inflammatory and immunologic conditions	Lower respiratory tract disorders (excl obstruction and infection)	Resp	44	22.248	17.226
Montelukast	Eosinophil count increased	White blood cell analyses	Haematology investigations (incl blood groups)	Inv	116	18.177	15.558
Montelukast	Cephalo-pelvic disproportion	Maternal complications of labour NEC	Maternal complications of labour and delivery	Preg	9	28.135	14.309
Montelukast	Sleep terror	Parasomnias	Sleep disorders and disturbances	Psych	133	15.228	13.155
Montelukast	Self esteem decreased	Personality disorders NEC	Personality disorders and disturbances in behaviour	Psych	59	15.305	12.185
Montelukast	Vasculitic rash	Skin vasculitides	Skin vascular abnormalities	Skin	15	18.706	10.426

Table 9. Data Mining Results with EB05 ≥ 2 for montelukast, by MedDRA Preferred Terms (sorted by Descending EB05 Scores) from approval to October 31, 2013							
Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Montelukast	Rheumatoid factor positive	Autoimmunity analyses	Immunology and allergy investigations	Inv	15	17.653	9.281
Montelukast	Nightmare	Parasomnias	Sleep disorders and disturbances	Psych	387	9.828	9.012
Montelukast	Morbid thoughts	Thinking disturbances	Disturbances in thinking and perception	Psych	47	11.384	8.384
Montelukast	Cutaneous vasculitis	Skin vasculitides	Skin vascular abnormalities	Skin	21	14.357	8.353
Montelukast	Asthma	Bronchospasm and obstruction	Bronchial disorders (excl neoplasms)	Resp	639	8.636	8.084
Montelukast	Suicidal ideation	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	935	8.41	7.965
Montelukast	Mood altered	Emotional and mood disturbances NEC	Mood disorders and disturbances NEC	Psych	300	8.717	7.905
Montelukast	Eosinophilia	Eosinophilic disorders	White blood cell disorders	Blood	140	8.48	7.328
Montelukast	Physical assault	Criminal activity	Legal issues	SocCi	52	9.26	7.083
Montelukast	Nasal polyps	Nasal disorders NEC	Upper respiratory tract disorders (excl infections)	Resp	15	14.526	6.946
Montelukast	Blood immunoglobulin E increased	Immunoglobulin analyses	Immunology and allergy investigations	Inv	33	10.094	6.918
Montelukast	Abnormal dreams	Parasomnias	Sleep disorders and disturbances	Psych	215	7.66	6.83
Montelukast	Mood swings	Fluctuating mood symptoms	Mood disorders and disturbances NEC	Psych	341	7.179	6.56
Montelukast	Vasculitis	Vasculitides NEC	Vascular inflammations	Vasc	104	7.723	6.53
Montelukast	Anger	Emotional and mood disturbances NEC	Mood disorders and disturbances NEC	Psych	402	7.087	6.522
Montelukast	Affective disorder	Mood disorders NEC	Mood disorders and disturbances NEC	Psych	76	7.941	6.5
Montelukast	Screaming	Speech articulation and rhythm disturbances	Communication disorders and disturbances	Psych	168	7.062	6.205
Montelukast	School refusal	Infancy, childhood and adolescence psychiatric disorders NEC	Psychiatric disorders NEC	Psych	24	9.252	5.923
Montelukast	Self-injurious ideation	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	56	7.235	5.743
Montelukast	Oppositional defiant disorder	Attention deficit and disruptive behaviour disorders	Cognitive and attention disorders and disturbances	Psych	28	8.088	5.607
Montelukast	Status asthmaticus	Bronchospasm and obstruction	Bronchial disorders (excl neoplasms)	Resp	21	9.091	5.606
Montelukast	Personality change	Behaviour and socialisation disturbances	Personality disorders and disturbances in behaviour	Psych	121	6.421	5.514
Montelukast	Educational problem	Educational issues	Lifestyle issues	SocCi	86	6.536	5.451

Table 9. Data Mining Results with EB05 ≥ 2 for montelukast, by MedDRA Preferred Terms (sorted by Descending EB05 Scores) from approval to October 31, 2013							
Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Montelukast	Feeling of despair	Mood alterations with depressive symptoms	Depressed mood disorders and disturbances	Psych	30	7.624	5.437
Montelukast	Aggression	Behaviour and socialisation disturbances	Personality disorders and disturbances in behaviour	Psych	761	5.76	5.424
Montelukast	Suicidal behaviour	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	45	6.802	5.263
Montelukast	Leukocytoclastic vasculitis	Skin vasculitides	Skin vascular abnormalities	Skin	39	6.799	5.153
Montelukast	Negative thoughts	Mood alterations with depressive symptoms	Depressed mood disorders and disturbances	Psych	27	7.194	5.07
Montelukast	Suicide attempt	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	341	5.486	5.015
Montelukast	Abnormal behaviour	Abnormal behaviour NEC	Psychiatric and behavioural symptoms NEC	Psych	773	5.117	4.821
Montelukast	Fear	Fear symptoms and phobic disorders (incl social phobia)	Anxiety disorders and symptoms	Psych	192	5.414	4.802
Montelukast	Homicidal ideation	Behaviour and socialisation disturbances	Personality disorders and disturbances in behaviour	Psych	66	5.722	4.653
Montelukast	Social avoidant behaviour	Behaviour and socialisation disturbances	Personality disorders and disturbances in behaviour	Psych	82	5.541	4.605
Montelukast	Crying	General signs and symptoms NEC	General system disorders NEC	Genrl	380	4.974	4.568
Montelukast	Depressed mood	Mood alterations with depressive symptoms	Depressed mood disorders and disturbances	Psych	166	5.18	4.552
Montelukast	Depression	Depressive disorders	Depressed mood disorders and disturbances	Psych	976	4.75	4.505
Montelukast	Product substitution issue	Product quality issues NEC	Product quality issues	Genrl	144	5.174	4.503
Montelukast	Attention deficit/hyperactivity disorder	Attention deficit and disruptive behaviour disorders	Cognitive and attention disorders and disturbances	Psych	97	5.286	4.461
Montelukast	Somnambulism	Parasomnias	Sleep disorders and disturbances	Psych	53	5.402	4.288
Montelukast	Mononeuropathy multiplex	Mononeuropathies	Peripheral neuropathies	Nerv	7	17.339	4.278
Montelukast	Vasculitis necrotising	Vasculitides NEC	Vascular inflammations	Vasc	12	8.456	4.266
Montelukast	Frustration	Emotional and mood disturbances NEC	Mood disorders and disturbances NEC	Psych	41	5.468	4.201
Montelukast	Pulmonary eosinophilia	Lower respiratory tract inflammatory and immunologic conditions	Lower respiratory tract disorders (excl obstruction and infection)	Resp	8	12.299	3.959
Montelukast	Sleep disorder	Sleep disorders NEC	Sleep disorders and disturbances	Psych	177	4.385	3.869
Montelukast	Parasomnia	Parasomnias	Sleep disorders and disturbances	Psych	10	8.301	3.837

Table 9. Data Mining Results with EB05 ≥ 2 for montelukast, by MedDRA Preferred Terms (sorted by Descending EB05 Scores) from approval to October 31, 2013							
Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Montelukast	Ear infection	Ear infections	Infections - pathogen unspecified	Infec	81	4.594	3.815
Montelukast	Irritability	General signs and symptoms NEC	General system disorders NEC	Genrl	339	4.173	3.814
Montelukast	Decreased interest	Mood alterations with depressive symptoms	Depressed mood disorders and disturbances	Psych	30	5.191	3.812
Montelukast	Middle insomnia	Disturbances in initiating and maintaining sleep	Sleep disorders and disturbances	Psych	63	4.601	3.725
Montelukast	Emotional disorder	Emotional and mood disturbances NEC	Mood disorders and disturbances NEC	Psych	180	4.176	3.689
Montelukast	Violence-related symptom	Behaviour and socialisation disturbances	Personality disorders and disturbances in behaviour	Psych	21	5.315	3.664
Montelukast	Intentional self-injury	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	79	4.416	3.659
Montelukast	Peak expiratory flow rate decreased	Respiratory and pulmonary function diagnostic procedures	Respiratory and pulmonary investigations (excl blood gases)	Inv	13	6.079	3.649
Montelukast	Self injurious behaviour	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	54	4.489	3.574
Montelukast	Thinking abnormal	Thinking disturbances	Disturbances in thinking and perception	Psych	117	4.102	3.516
Montelukast	Obsessive-compulsive disorder	Obsessive-compulsive disorders and symptoms	Anxiety disorders and symptoms	Psych	59	4.346	3.494
Montelukast	Antineutrophil cytoplasmic antibody positive	Autoimmunity analyses	Immunology and allergy investigations	Inv	9	7.477	3.448
Montelukast	Enuresis	Bladder and urethral symptoms	Urinary tract signs and symptoms	Renal	44	4.369	3.392
Montelukast	Excessive eye blinking	Eyelid movement disorders	Ocular neuromuscular disorders	Eye	22	4.798	3.344
Montelukast	Lung infiltration	Parenchymal lung disorders NEC	Lower respiratory tract disorders (excl obstruction and infection)	Resp	74	4.017	3.308
Montelukast	Poor quality sleep	Sleep disturbances NEC	Sleep disturbances (incl subtypes)	Nerv	42	4.284	3.306
Montelukast	Obsessive thoughts	Obsessive-compulsive disorders and symptoms	Anxiety disorders and symptoms	Psych	21	4.744	3.278
Montelukast	Pulmonary vasculitis	Lower respiratory tract inflammatory and immunologic conditions	Lower respiratory tract disorders (excl obstruction and infection)	Resp	6	13.14	3.199
Montelukast	Rhinitis allergic	Nasal congestion and inflammations	Upper respiratory tract disorders (excl infections)	Resp	20	4.625	3.168
Montelukast	Anxiety	Anxiety symptoms	Anxiety disorders and symptoms	Psych	699	3.357	3.154
Montelukast	Mental disorder	Mental disorders NEC	Psychiatric disorders NEC	Psych	101	3.703	3.137
Montelukast	Social problem	Social issues NEC	Lifestyle issues	SocCi	17	4.717	3.124

Table 9. Data Mining Results with EB05 ≥ 2 for montelukast, by MedDRA Preferred Terms (sorted by Descending EB05 Scores) from approval to October 31, 2013							
Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Montelukast	Asthmatic crisis	Bronchospasm and obstruction	Bronchial disorders (excl neoplasms)	Resp	17	4.702	3.115
Montelukast	Red blood cell sedimentation rate increased	Haematological analyses NEC	Haematology investigations (incl blood groups)	Inv	53	3.917	3.112
Montelukast	Ear pain	Ear disorders NEC	Aural disorders NEC	Ear	55	3.802	3.033
Montelukast	Adverse event	Therapeutic and nontherapeutic responses	Therapeutic and nontherapeutic effects (excl toxicity)	Genrl	102	3.565	3.022
Montelukast	Impatience	Behaviour and socialisation disturbances	Personality disorders and disturbances in behaviour	Psych	11	5.05	2.985
Montelukast	Forced expiratory volume decreased	Respiratory and pulmonary function diagnostic procedures	Respiratory and pulmonary investigations (excl blood gases)	Inv	8	5.892	2.896
Montelukast	Panic attack	Panic attacks and disorders	Anxiety disorders and symptoms	Psych	95	3.329	2.805
Montelukast	Pre-eclampsia	Hypertension associated disorders of pregnancy	Maternal complications of pregnancy	Preg	18	4.146	2.783
Montelukast	Breech presentation	Foetal position and presentation abnormalities	Foetal complications	Preg	11	4.598	2.743
Montelukast	Completed suicide	Suicidal and self-injurious behaviour	Suicidal and self-injurious behaviours NEC	Psych	176	3.074	2.712
Montelukast	Agoraphobia	Fear symptoms and phobic disorders (incl social phobia)	Anxiety disorders and symptoms	Psych	10	4.676	2.709
Montelukast	Wheezing	Bronchospasm and obstruction	Bronchial disorders (excl neoplasms)	Resp	97	3.199	2.701
Montelukast	Exposure during pregnancy	Exposures associated with pregnancy, delivery and lactation	Exposures, chemical injuries and poisoning	Inj&P	40	3.506	2.688
Montelukast	Initial insomnia	Disturbances in initiating and maintaining sleep	Sleep disorders and disturbances	Psych	33	3.534	2.638
Montelukast	Tourette's disorder	Neurological disorders congenital NEC	Neurological disorders congenital	Cong	18	3.793	2.548
Montelukast	Vocal cord disorder	Laryngeal and adjacent sites disorders NEC (excl infections and neoplasms)	Upper respiratory tract disorders (excl infections)	Resp	11	4.212	2.523
Montelukast	Social phobia	Fear symptoms and phobic disorders (incl social phobia)	Anxiety disorders and symptoms	Psych	9	4.467	2.516
Montelukast	Fear of death	Fear symptoms and phobic disorders (incl social phobia)	Anxiety disorders and symptoms	Psych	10	4.25	2.479
Montelukast	Peroneal nerve palsy	Mononeuropathies	Peripheral neuropathies	Nerv	18	3.671	2.466
Montelukast	Insomnia	Disturbances in initiating and maintaining sleep	Sleep disorders and disturbances	Psych	518	2.621	2.437
Montelukast	Hallucination	Perception disturbances	Disturbances in thinking and perception	Psych	230	2.716	2.434

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Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
Montelukast	Agitation	Anxiety symptoms	Anxiety disorders and symptoms	Psych	302	2.659	2.417
Montelukast	Sputum abnormal	Respiratory tract and thoracic histopathology procedures	Respiratory and pulmonary investigations (excl blood gases)	Inv	8	4.349	2.362
Montelukast	Fight in school	Educational issues	Lifestyle issues	SocCi	9	4.123	2.335
Montelukast	Disturbance in attention	Mental impairment (excl dementia and memory loss)	Mental impairment disorders	Nerv	159	2.649	2.322
Montelukast	Sleep talking	Parasomnias	Sleep disorders and disturbances	Psych	12	3.751	2.301
Montelukast	Dysaesthesia	Paraesthesias and dysaesthesias	Neurological disorders NEC	Nerv	10	3.909	2.286
Montelukast	Limb reduction defect	Musculoskeletal and connective tissue disorders of limbs congenital	Musculoskeletal and connective tissue disorders congenital	Cong	8	4.102	2.241
Montelukast	Abnormal labour	Maternal complications of labour NEC	Maternal complications of labour and delivery	Preg	6	4.877	2.235
Montelukast	Nasal congestion	Nasal congestion and inflammations	Upper respiratory tract disorders (excl infections)	Resp	68	2.71	2.213
Montelukast	Hepatitis cholestatic	Cholestasis and jaundice	Hepatic and hepatobiliary disorders	Hepat	22	3.165	2.21
Montelukast	Abortion	Abortions not specified as induced or spontaneous	Abortions and stillbirth	Preg	13	3.517	2.201
Montelukast	Sinusitis	Upper respiratory tract infections	Infections - pathogen unspecified	Infec	131	2.544	2.199
Montelukast	Pregnancy	Normal pregnancy, labour and delivery	Pregnancy, labour, delivery and postpartum conditions	Preg	95	2.609	2.198
Montelukast	Gun shot wound	Non-site specific injuries NEC	Injuries NEC	Inj&P	12	3.566	2.189
Montelukast	Panic disorder	Panic attacks and disorders	Anxiety disorders and symptoms	Psych	14	3.437	2.188
Montelukast	Conversion disorder	Somatoform disorders	Somatoform and factitious disorders	Psych	21	3.152	2.182
Montelukast	Product taste abnormal	Product physical issues	Product quality issues	Genrl	15	3.31	2.141
Montelukast	Restlessness	Increased physical activity levels	Changes in physical activity	Psych	103	2.515	2.134
Montelukast	Henoch-Schonlein purpura	Purpura and related conditions	Skin vascular abnormalities	Skin	17	3.207	2.13
Montelukast	Polyneuropathy	Acute polyneuropathies	Peripheral neuropathies	Nerv	21	3.072	2.127
Montelukast	Anxiety disorder	Anxiety disorders NEC	Anxiety disorders and symptoms	Psych	12	3.457	2.122
Montelukast	Paraesthesia	Paraesthesias and dysaesthesias	Neurological disorders NEC	Nerv	264	2.331	2.104
Montelukast	Atonic seizures	Seizures and seizure disorders NEC	Seizures (incl subtypes)	Nerv	8	3.818	2.094
Montelukast	Tic	Tic disorders	Changes in physical activity	Psych	83	2.499	2.08
Montelukast	Tearfulness	Mood alterations with depressive	Depressed mood disorders and disturbances	Psych	19	3.058	2.077

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Generic name	**Preferred Term**	**High Level Term**	**High Level Group Term**	**System Organ Class**	**N**	**EBGM**	**EB05**
		symptoms					
Montelukast	Sinus headache	Headaches NEC	Headaches	Nerv	17	3.115	2.069
Montelukast	Placental disorder	Placental abnormalities (excl neoplasms)	Placental, amniotic and cavity disorders (excl haemorrhages)	Preg	10	3.524	2.064
Montelukast	Hallucination, visual	Perception disturbances	Disturbances in thinking and perception	Psych	67	2.532	2.064
Montelukast	Upper-airway cough syndrome	Upper respiratory tract signs and symptoms	Respiratory disorders NEC	Resp	13	3.288	2.058
Montelukast	Abortion spontaneous	Abortions spontaneous	Abortions and stillbirth	Preg	83	2.471	2.057
Montelukast	Collagen disorder	Connective tissue disorders (excl LE)	Connective tissue disorders (excl congenital)	Musc	6	4.186	2.039
Montelukast	Abnormal sleep-related event	Parasomnias	Sleep disorders and disturbances	Psych	8	3.689	2.025
Montelukast	Sinus disorder	Paranasal sinus disorders (excl infections and neoplasms)	Upper respiratory tract disorders (excl infections)	Resp	22	2.893	2.02